Original article

Title: High-intensity interval training before elective abdominal aortic aneurysm repair: A randomised controlled feasibility trial

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Abstract

Background: This study assessed the feasibility of a pre-operative high-intensity interval training (HIT) programme in patients undergoing elective AAA repair.

Methods: In this feasibility trial, participants were allocated by minimisation to pre-operative HIT (n=27) or usual care (n=26). The HIT group were offered three exercise sessions per week for 4 weeks, and weekly maintenance sessions if surgery was delayed. Feasibility and acceptability outcomes were rates of screening, eligibility, recruitment, retention, outcome completion, adverse events, and exercise adherence. Data on exercise enjoyment (PACES), cardiorespiratory fitness (anaerobic threshold and peak oxygen uptake), quality of life, post-operative morbidity and mortality, duration of hospital stay, and healthcare utilisation were also collected.

Results: Screening, eligibility, recruitment, retention, and outcome completion rates were 100% (556/556), 43% (240/556), 22% (53/240), 91% (48/53), and 79-92%, respectively. Overall exercise session attendance was 76% (276/364), and the mean post-programme PACES score was 98/119 ('enjoyable'; SD 19); however, the intensity of exercise was generally lower than that intended. Mean anaerobic threshold after exercise training (adjusted for baseline score and minimisation variables) was 11.9 mL/kg/min in exercise versus 11.6 mL/kg/min in control (difference = 0.3 mL/kg/min; 95% CI, -0.4 to 1.1). There were trivial-to-small differences in post-operative clinical and patient-reported outcomes between the exercise and control groups.

Conclusions: Despite the intensity of exercise being generally lower than intended, the findings support the feasibility and acceptability of both pre-operative HIT and the trial procedures. An appropriately-powered, multi-centre trial is required to establish the clinical and cost-effectiveness of the intervention.

Registration number: ISRCTN09433624 (https://www.isrctn.com/).

Introduction

Abdominal aortic aneurysms (AAAs) are found in 5–7.5% of men and 1.5–3% of women aged ≥65 years,[1] usually remaining asymptomatic until they rupture. Rupture of an AAA causes huge internal bleeding and carries an overall mortality in excess of 80%.[2] Elective open surgical or endovascular repair of the AAA is the most effective treatment for preventing aneurysm-related rupture and death; it is usually reserved for AAAs ≥5.5 cm diameter,[3] with more than 4,000 elective AAA repairs performed in the United Kingdom (UK) each year.[4] However, elective aortic surgery also carries significant risk. For example, data from the UK in 2014 indicate in-hospital mortality rates of 3.2% and 0.8% for open and endovascular aneurysm repair, respectively,[4] with non-fatal post-operative complications several times more common.[5-7]

Aneurysm repair, especially open surgery, results in neuroendocrine, metabolic and inflammatory changes leading to an increase in global tissue oxygen uptake of up to 50%.[8] Patients with low cardiorespiratory fitness are less able to meet these extra demands perioperatively, which may lead to tissue hypoxia and debilitative or life-threatening complications. This notion is supported by observational studies showing an association between pre-operative cardiorespiratory fitness and mortality and major morbidity following elective AAA repair.[9-12] Up to half of patients presenting for intra-abdominal surgery do not have the pre-requisite fitness, quantified using cardiopulmonary exercise testing, to be deemed 'low risk' for perioperative complications.[13] It is therefore intuitive that improving cardiorespiratory fitness prior to surgery will translate to reduced complications following major surgery.

To date the clinical and cost-effectiveness of preoperative exercise training has yet to be established prior to AAA repair through a large multi-centre trial. Under such circumstances pilot and feasibility studies are often appropriate as part of a phased approach to the development, testing and evaluation of healthcare interventions. [14, 15] During protocol development, the project team were

unaware of any published or on-going studies in this respect. Two small studies had demonstrated that moderate-intensity exercise training was feasible and could improve cardiorespiratory fitness in people *under surveillance* for a small AAA.[16, 17] However, it was unclear whether meaningful cardiorespiratory fitness improvements could be safely achieved in patients with a large AAA in the limited window available before surgery (typically 4-6 weeks).[18-20]

High-intensity interval training (HIT), which is characterised by brief (e.g., 1-4 minute) bouts of vigorous exercise (e.g., running, cycling) interspersed by periods of passive or active recovery, represents an attractive approach in this context. Indeed, a recent meta-analysis of 6 trials (n=229) demonstrated a greater improvement in peak oxygen uptake following HIT when compared with moderate-intensity continuous training in patients with coronary artery disease.[21] However, the absence of HIT studies involving our target population or setting (UK National Health Service [NHS]) made it difficult to draw inferences about the likely success of a definitive trial. Therefore, it was concluded that a randomised feasibility trial of pre-operative HIT versus usual care (no exercise) for people awaiting elective AAA repair was required.

The overall aims of the High-intensity Interval Training before Abdominal Aortic Aneurysm repair (HIT-AAA) study were to assess whether HIT is a feasible and acceptable intervention for the pre-surgical optimisation of AAA patients (i.e., examine intervention implementation potential) and to test the feasibility of the protocol design (i.e., examine methodological standard). Thus, the main purpose of the study was to assess whether it was appropriate to progress to a larger-scale trial and, if so, to optimise the design and conduct of any such trial. Accordingly, this manuscript reports on rates of screening, eligibility, recruitment, retention, outcome completion, exercise adherence, and adverse events, as well as reasons for exclusion and non-consent, sample characteristics, and the distribution of potential primary outcomes. For completeness, preliminary data on effectiveness and health care resource use are also presented.

Methods

A full description of methods is available in a previously published protocol paper.[22] The study was a two-arm, parallel-group, randomised controlled feasibility trial conducted in three teaching hospitals in England (James Cook University Hospital, Middlesbrough [Site 1]; Northern General Hospital, Sheffield [Site 2]; York Hospital, York [Site 3]). Ethics approval was granted by the North East-Tyne & Wear South Research Ethics Committee (Ref: 13/NE/0116), and all participants provided written informed consent prior to enrolment. The trial was prospectively registered (Current Controlled Trials ISRCTN09433624).

Participants

Participants were recruited from vascular surgical or pre-operative assessment clinics at each of the trial sites. Patients aged ≥18 years that had been listed, following routine clinical assessment and vascular multidisciplinary team consideration, for an open or endovascular repair of a 5.5–7.0 cm diameter infra-renal AAA were invited to participate. Exclusion criteria were refusal or inability to provide informed consent, non-operatively managed AAA, non infra-renal aneurysm anatomy (juxta-renal, supra-renal or thoracic), infra-renal AAA diameter >7.0 cm, emergency AAA repair, contraindication to exercise testing or training,[23] specialist referral required (e.g., to cardiology), and body mass index <20 or >40 kg/m^2.

Randomisation and concealment

Following baseline assessment, participants were allocated using minimisation to receive either usual care alone (control) or usual care plus a pre-operative exercise programme. There were three minimisation factors: sex, type of procedure (open or endovascular repair), and study centre. Allocation was concealed from those assessing eligibility and recruiting patients, with eligible patients allocated remotely via e-mail by the trial statistician (A.M.B.). The research nurses in charge

of recruitment were unaware of the specific minimisation factors and so could not deduce future group assignments by keeping track of the previous allocations. Minimisation was performed using the Minim software[23] with a 1:1 allocation ratio and equal weighting for the three minimisation factors.

Interventions

All participants received usual care, which comprised evidence-based medical optimisation. Participants allocated to the exercise group were also invited to complete three hospital-based, exercise sessions per week, for the four consecutive weeks (i.e., weeks 1-4; 'main phase') immediately preceding their intended operation date (in week 5). Participants whose operation was delayed beyond week 5 (e.g., due to unavailability of a hospital bed) also received a maintenance phase of training (one exercise session per week). All exercise was undertaken on a cycle ergometer (Optibike Med, Ergoline, Germany). Each of the first three sessions comprised a 10-minute warm-up of unloaded cycling, 8 × 2-minute intervals of high-intensity cycling interspersed with 2-minute rest periods of unloaded cycling, and then a 5-minute cool-down of unloaded cycling. In all subsequent sessions, participants had the choice of performing 8 × 2-minute or 4 × 4-minute "work" intervals for the main body of the workout. In the first exercise session, the 2-minute work intervals were performed at the power output corresponding to anaerobic threshold on a baseline cardiopulmonary exercise test (CPET). The power output in all subsequent sessions was guided by participants' ratings of perceived exertion (RPE), which were assessed separately for legs (RPE-L) and breathlessness/chest (RPE-C) at the end of each interval using Borg's CR-10 scale.[24] The aim was for all work intervals to be undertaken at a "hard" to "very hard" level of exertion (RPE-L or RPE-C = 5 and 7, respectively). However, for safety reasons, the power output of the work intervals was reduced if systolic blood pressure (measured manually via sphygmomanometer at the end of each interval) exceeded 180 mmHg or if heart rate (recorded continuously via telemetry: Polar RS400, Kempele, Finland) exceeded 95% of the maximum observed on baseline CPET. We recorded all

occurrences of power output reduction due to safety criteria, and all exercise-related adverse events. Each session was directly supervised by a research nurse and a physiotherapist who were trained in immediate life support, with full resuscitation equipment immediately available. Sessions were also intermittently attended by one of two experienced exercise scientists (G.A.T., M.W.) who had overall responsibility for ensuring treatment fidelity of the exercise programme.

Study schedule and assessments

Figure 1 provides an overview of the assessment schedule. A baseline assessment visit was conducted in week 0, during which the following were recorded: medical history, current medications, baseline characteristics, maximum AAA diameter (transabdominal ultrasound), cardiorespiratory fitness (anaerobic threshold and peak oxygen uptake recorded during an incremental cycle ergometer test to maximum volitional exertion), health-related quality of life (SF-36v2 physical function [PF] and mental health [MH] sub-scales,[25] EQ-5D-5L utility index and EQ-visual analogue scale[26]), and preference for allocation to exercise or control.

In week 5, 24–48 hours before the planned operation date, participants attended for re-assessment of cardiorespiratory fitness and quality of life. Anaerobic threshold was determined by two experienced investigators blinded to group allocation, as described previously.[27] The exercise group also provided an overall rating of enjoyment of the exercise programme, using the Physical Activity Enjoyment Scale (PACES),[28] as well as having their maximum AAA diameter re-assessed.

Surgical repairs were performed by the open or endovascular route, as per routine clinical practice in each institution. Surgery was planned in week 5 (breeches recorded) with members of the clinical teams blinded to group allocation. During the in-hospital, post-operative period, an investigator blinded to group allocation recorded data on the following: organ-specific morbidity (Post-Operative Morbidity Survey [POMS],[7] recorded daily), mortality, and durations of critical care and hospital stay.

Following hospital discharge, participants were asked to record their healthcare usage for a 12-week period using a structured diary (see online-only Data Supplement). At 6 weeks post-discharge, participants received a telephone call from a study investigator encouraging accurate diary completion. Research nurses retrieved this information from participants via a face-to-face visit conducted at 12 weeks post-discharge. Health-related quality of life (SF-36 and EQ-5D) was also reassessed at this visit.

Feasibility and acceptability outcomes

Outcomes used to assess the feasibility and acceptability of key trial parameters were rates of:

- Screening
- Eligibility – calculated by dividing the number of people who met eligibility criteria by the number of people screened for eligibility
- Recruitment – calculated by dividing the number of participants allocated to exercise or control by the number of people who were eligible for the study
- Retention – calculated by dividing the number of participants who completed the study by the number recruited
- Outcome completion – defined as the number of participants providing usable data for the different outcomes at each study time-point
- Exercise adherence – calculated by dividing the total number of attended sessions by the total number of scheduled sessions. We also determined the number of participants who were adherent (herein described as 'adherent' participants), as defined by completing ≥75% of the 'main-phase' sessions (i.e., ≥9/12 sessions), plus all weekly maintenance sessions if surgery was delayed.
- Adverse events – these were recorded on a local site adverse event log. Events were classified according to severity and their relatedness to study intervention.

Group preference and reasons for exclusion and non-consent were recorded, and data on sample characteristics and the distribution of potential primary outcomes were also collected.

Sample size

The aim of the study was not to provide a definitive estimate of treatment effect, so the sample size calculation, which is described in the online Data Supplement, was based on exercise adherence rather than a clinical or patient-reported outcome. The aim was to recruit at least 50 participants within a 21-month recruitment period.

Analysis of clinical and patient-reported outcomes

For all clinical and patient-reported outcomes, point estimates and their uncertainty are presented as an indication of the range of effect sizes consistent with the data. No robust inference has been attempted, as this was a feasibility study that was not powered to detect small yet clinically meaningful effects. For cardiorespiratory fitness at week 5, a conventional ANCOVA model was used to estimate the mean difference between groups in anaerobic threshold and peak oxygen uptake, adjusted for baseline score, operative procedure and trial site. Although sex was a minimisation factor, it was not included as a factor in the analysis as the sample was almost exclusively male. Inter-individual differences in the fitness response to the exercise programme (treatment heterogeneity) were also quantified, as described in the online Data Supplement.

For morbidity, a linear mixed model was used to explore differences between groups in total POMS score (score out of 9). The model included operative procedure and trial site, fixed effects for group and number of days post-operation, and a day × group interaction term. For length of hospital stay we derived the median in days (interquartile range) in each group, together with the hazard ratio (exercise vs. control) for 'discharge alive' using Cox regression, adjusting for operative procedure and

trial site. For the EQ-5D utility index, EQ-visual analogue scale (EQ-VAS), and SF-36 PF and MH sub-scales at week 5 and 12 weeks after hospital discharge, a linear mixed model was used with restricted maximum likelihood, adjusted for baseline score, operative procedure and trial site. This model included all three time-points in the same analysis – a principled method for handling any data missing at random on the dependent variable.[29] All effects are presented with 95% confidence intervals (CI).

Economic evaluation

A prospective economic evaluation was rehearsed to develop and refine the methods for a subsequent definitive trial. The methods for this evaluation are described in the online Data Supplement.

Results

Figure 2 shows the flow of participants through the trial. Recruitment took place between September 2013 and July 2015, with all follow-up data collection completed by January 2016. The trial was stopped at the end of the grant funding period with the target sample size having been achieved.

Screening, eligibility and recruitment

All potentially-eligible AAA patients were screened during the recruitment period, giving a screening rate of 100%. Of 556 patients screened for participation, 240 met eligibility criteria and 53 were recruited, giving eligibility and recruitment rates of 43% and 22%, respectively. Sites 1, 2 and 3 recruited 24, 21 and 8 participants, respectively. Reasons for non-consent and exclusion are shown in Figure 2, the most common of which were social reasons (e.g., work commitments or difficulty travelling; n=78), AAA diameter >7 cm (n=78), and non infra-renal AAA anatomy (n=66).

Group allocation, group preference and participant characteristics

Twenty-seven participants were allocated to exercise and 26 to usual care. Of the 47 participants who expressed a preference for a specific group before allocation, 30 (64%) preferred exercise. Fifty men (94%) and 3 women (6%) were recruited to the study. Participant characteristics at baseline are shown in Table 1; the groups were well balanced for the majority of variables. Eleven participants from each group underwent open surgical AAA repair, whereas 16 (59%) from the exercise group and 15 (58%) from the usual care group received endovascular AAA repair.

Retention

The retention rate was 91%. Five out of 53 participants formally left the study (three exercise, two control). One person from each group withdrew due to no longer undergoing surgery, one control participant withdrew after declining surgery, one exercise participant withdrew before having completed any sessions due to expedited surgery, and one exercise participant withdrew after completing just one exercise session. In the latter case, the participant reported feeling unwell approximately 8 hours following the exercise session. They subsequently underwent a cardiology assessment which showed no abnormality however, they decided to withdraw from the study at that stage.

Exercise adherence, exercise enjoyment and safety data

A detailed description of the training data has been presented elsewhere.[30] Of the 27 exercise participants, 15 had a delayed operation and therefore required at least one maintenance exercise session (range attended 0 to 9). No surgical delays occurred because of the exercise programme; rather, the main reason for delayed operations was a lack of hospital bed availability for postoperative care on the day of surgery. In total, 324 ‘main-phase’ and 40 maintenance exercise sessions were scheduled, of which 240 (74%) and 36 (90%) were completed, respectively (overall attendance rate = 76%). Seventeen of the 27 exercise participants (63%, 95% CI 45 to 81%) achieved

the pre-specified adherence criterion. Three participants did not complete any sessions: two declined the exercise programme and one had expedited surgery. In addition, two participants did not complete the exercise programme: one was a 'full withdrawal' after completing one session and referral to cardiology (described above); the other was a 'withdrawal from exercise' after completing five sessions and referral to cardiology. This latter participant experienced prodromal symptoms (dizziness) on four separate occasions when the power output was increased beyond approximately 80 W. These symptoms resolved quickly upon power output reduction, with the participant completing the exercise sessions. Subsequent investigator review of the participant's baseline CPET resulted in a cardiology review to exclude significant underlying cardiac pathology. This review was normal; however, the participant was withdrawn from the exercise programme for logistical reasons.

The intensity of all work intervals completed by the 17 'adherent' participants is summarised as follows: mean RPE-L 4.1 (SD 2.0); mean RPE-C 3.5 (SD 1.9); mean heart rate 81.7 (SD 8.5) %max; and 30% of work intervals being reported in the "hard" to "very hard" range (RPE-L 5 to 7). The mean improvement in cycling power output from baseline to week 4 sessions for all participants was 8 W. The mean PACES score was 98 out of 119 (SD 19), equating to participants reporting the exercise sessions as 'enjoyable'.

Twenty of the 27 exercise participants had at least one occurrence of cycling power output reduction due to safety criteria (e.g., systolic blood pressure >180 mmHg) being 'triggered'. Of all work intervals, there were 36 instances of power output reduction in the 17 'adherent' participants, and 40 instances in the 10 'non-adherent' participants (incidence rates of 2.6% and 10.1%, respectively). One adverse event occurred that resulted in the termination of an exercise session: a single episode of short-lived angina that was relieved through self-administration of glyceryl trinitrate. Twenty-two

exercise participants had maximal AAA diameter measurements at both baseline and week 5; giving mean values of 6.0 (SD 0.4) cm and 5.9 (SD 0.4) cm, respectively.

A summary of the feasibility and acceptability data is presented in Table 2.

Cardiorespiratory fitness

A week 5 anaerobic threshold value was available for 46 participants (22 exercise, 24 control), of which one control participant had a missing baseline value, which we imputed using mean imputation.[31] The anaerobic threshold at week 5 was 11.7 mL/kg/min in the exercise group and 11.4 mL/kg/min in the control group (difference = 0.3 mL/kg/min; 95% CI, -0.4 to 1.1). The SD for individual differences in response to the exercise programme was 1.0 mL/kg/min (95% CI -0.7 to 1.5) – a moderate effect size indicating potentially substantial inter-individual differences in treatment response. For exercise vs. control, assuming a minimum clinically important difference of 1.5 mL/kg/min, one individual was very likely to be a positive responder, 3 were likely to be positive responders, 7 were possibly positive responders, 8 were trivial (non-) responders, and 3 were possibly negative responders.

A week 5 peak oxygen uptake value was available for 47 participants (23 exercise, 24 control). Peak oxygen uptake at week 5 was 16.8 mL/kg/min in the exercise group vs. 16.3 mL/kg/min in the control group (difference = 0.5 mL/kg/min, 95% CI -0.6 to 1.7). There was no evidence of substantial inter-individual response to exercise.

Post-operative morbidity and mortality

POMS data was collected for all 48 participants who completed the study. Mean total POMS count up to the point of discharge from hospital was 2.3 in the exercise group vs. 2.1 in the control group (difference = 0.2, 95% CI -0.3 to 0.7). There was no substantial group × post-operative day

interaction. For example, at day 1 post-operation, the mean total POMS count was 3.7 in exercise vs. 3.4 in control. At days 3 and 5 post-operation, the POMS counts were 2.4 vs. 2.3 and 1.3 vs. 1.2, respectively. There were no in-hospital or 30-day deaths in either group. One participant from the exercise group died 12 weeks after hospital discharge due to a myocardial infarction.

Length of hospital stay

Unadjusted median (IQR) length of hospital stay was 7 (4.5 to 8.5) days in the exercise group vs. 6 (4 to 8) days in the control group (n = 48). The hazard ratio for alive-discharge in exercise vs. control was 0.96 (95% CI, 0.53 to 1.74).

Health-related quality of life

EQ-5D utility scores were available for 49 participants at week 5 (25 exercise, 24 control) and 43 participants at 12 weeks post-discharge (21 exercise, 22 control). The mean EQ-5D utility index at week 5 was 0.864 in exercise vs. 0.796 in control (difference = 0.068, 95% CI 0.002 to 0.135). At 12 weeks post-discharge, the mean EQ-5D utility index was 0.837 in exercise vs. 0.760 in control (difference = 0.077, 95% CI 0.005 to 0.148). The mean EQ-5VAS score at week 5 was 81.9 in the exercise group vs. 75.8 in control (difference = 6.1; 95% CI, -0.3 to 12.6). At week 12 post-discharge, the mean EQ-VAS score was 79.6 in exercise vs. 74.4 in control (difference = 5.2, 95% CI -1.7 to 12.0).

A SF-36 PF score was available for 48 participants at week 5 (24 exercise, 24 control) and 43 participants at 12 weeks post-discharge (22 exercise, 21 control). The mean SF-36 PF score at week 5 was 49.6 in exercise vs. 49.9 in control (difference = -0.3, 95% CI -2.7 to 2.1). At 12 weeks post-discharge, the mean SF-36 PF scores were 49.4 and 46.5, respectively (difference = 2.9, 95% CI 0.4 to 5.4). A SF-36 MH score was available for 49 participants at week 5 (25 exercise, 24 control) and 42 participants at 12 weeks post-discharge (21 exercise, 21 control). The mean SF-36 MH score at week 5 was 54.6 in exercise vs. 55.1 in control (difference = -0.5, 95% CI -3.3 to 2.3). At 12 weeks post-

discharge, the mean SF-36 MH scores were 55.6 and 55.0, respectively (difference = 0.6, 95% CI -2.4 to 3.6).

Health economic data

There was no missing data for the costs of the exercise programme and the AAA repair procedures. The costs of the exercise programme are presented in the online Data Supplement; the mean cost per participant was £1,176. Unit costs for open and endovascular AAA repair procedures (including resource inputs during hospital stay) were based on NHS National Tariff Schedules: £8,285.56 and £12,675.50, respectively.[32]

Data on health and social care costs after hospital discharge were available from 43 participants (21 exercise, 22 control). The average costs per participant for each cost category at follow-up are shown in the online Data Supplement. Data regarding personal costs to each trial participant including informal care-givers time was not included due to the unreliability of the data. Hospital re-admission (due to any cause) was the highest resource use category across all categories in the study. There were no hospital re-admissions in the exercise group, and three in the control group (due to shortness of breath, rectal bleeding, and oesophageal varices). The costs of out-patient visits were also a high cost category across both study arms; however, it must be noted that the costs of any diagnostic tests conducted at these visits were included. The cost of district nursing was also notably high in the exercise group: this was due to one participant recording 17 visits in the first 3 weeks of follow-up.

The average total cost per participant for each group is presented in Table 3. The mean total cost in the exercise group per participant was £12,519 vs. £12,010 in control (bootstrapped mean difference = £510, 95% CI -1,393 to 2,498).

Discussion

This study successfully tested recruitment and group allocation procedures, the logistics of study measurements and follow-up, and the feasibility and preliminary effectiveness of a pre-operative HIT programme in people awaiting elective AAA repair. A key finding was that the trial procedures were mostly feasible. The pre-operative HIT programme was also generally feasible and acceptable; however, exercise progression was often limited by the safety criteria, which resulted in an inconsistent and lower-than-prescribed intensity of exercise. This issue may have contributed to the observation that cardiorespiratory fitness did not change substantially at the group level, although there was evidence of inter-individual heterogeneity, with half of the exercise participants possibly-to-very likely being positive responders (improvement in anaerobic threshold >1.5 mL/kg/min). The findings also indicate a potential small beneficial effect of the exercise programme on health status and physical function up to 12 weeks post discharge. Herein, the main lessons that have been learnt about the potential usefulness of a future definitive trial are discussed, as well as how study procedures could be improved to maximise the chances of a future trial being successful.

The feasibility and acceptability of pre-operative HIT in people with a large AAA was a key area of uncertainty prior to conducting this work. The participant characteristics are consistent with those of a high-risk, elderly and unfit population, and there was insufficient relevant literature to inform if such patients would engage with this intervention or if they could complete it safely. Overall, the findings generally support the feasibility and acceptability of the intervention. For example, recruitment was to time and target, there were few post-randomisation withdrawals, and post-programme ratings of enjoyment were high. The preliminary safety data was also favourable in that there were few adverse events and no evidence of aneurysm expansion due to exercise. Although data were not collected from non-consenting patients to allow a comparison of their characteristics with those of trial participants, the participants' fitness data was comparable to that observed in routine pre-operative assessment.[33] Therefore, any potential concern about recruitment bias in

favour of physically-active patients does not seem to be supported by the data. Finally, the overall session attendance rate was good at 76%. The trial protocol specified a success criterion of a lower limit of the 90% CI of 67% for the proportion of the exercise group meeting the pre-specified adherence criterion.[22] Strictly, inasmuch as only 17 of the 27 exercise participants (63%) were adherent, this criterion was not met. The current study did not employ any specific adherence-enhancing components in the intervention, however, cognitive-behavioural strategies could easily be utilised as part of any future trial to optimise exercise adherence thereby increasing the likelihood of success.

It is also important to consider the practicality of intervention delivery, because this will help inform future trial procedures as well as assessing the likelihood of the exercise programme being implemented as part of routine pre-operative care and as a future commissioned service. In the context of the UK healthcare system, it was essential that the intervention did not interfere with the national target of patients being operated on within 8 weeks of referral.[34] All participants completing the exercise programme did so within this treatment window with no surgical delays consequent to this. The exercise programme was also generally considered easy to deliver, owing to its relatively simple design. However, two issues were identified. Firstly, the research nurses perceived it burdensome to take manual blood pressure readings at the end of every work interval. The authors felt this practice to be necessary given the lack of published evidence on exercise for people with a large AAA. In future trials, it seems reasonable to suggest that the frequency of blood pressure recordings could be reduced. Besides making the intervention more practical to deliver, this could potentially lead to a marked reduction in intervention delivery costs because sessions could then feasibly be delivered by a single healthcare professional. Regarding costs, although additional resources (e.g., staff, equipment) would be required to offer a pre-operative exercise service, the overall additional costs are likely to be modest, lower than that reported in Table 3, and not markedly different from the cost of running a physiotherapy-led cardiac rehabilitation service. A

second and key issue regarding intervention delivery was that the intensity of exercise, as predominantly indicated by RPE, was generally inconsistent and lower than prescribed. Although the possibility of participant under-reporting of RPE cannot be excluded, this finding is more likely explained by exercise progression being limited by the exercise safety criteria. Indeed, most (74%) participants had at least one occurrence of cycling power output reduction due to a safety criterion being 'triggered'. This observation is important because sub-optimal exercise progression may limit adaptations in cardiorespiratory fitness, which in turn may limit the potential for improvements in post-operative outcomes to be observed relative to control. Although not based on empirical evidence, the authors encourage a conservative approach with this population that includes thorough pre-participation screening, direct exercise supervision with immediate access to first aid/life support equipment, and tailoring of the exercise prescription according to individual perceptual and physiological responses.

The HIT-AAA feasibility trial was essentially a small version of a full-scale trial; what is sometimes referred to as an external pilot trial.[35] A benefit of this design was that it allowed us to test whether the components of the main trial could all work together. Overall, there were no major difficulties identified in the design or implementation of any of the trial procedures. For example, the minimisation process worked smoothly and yielded equality in groups, the blinding procedures ran as intended, and the rates of retention and outcome completion were good. One potential area of concern for a future trial is the lower completion rates for the post-discharge questionnaires/diaries. Here, missing data approached 20%; the level above which there may be threats to trial validity.[36] Feedback from participant interviews suggests that burden is a factor and that lengthy or repetitive questionnaires may impact completion rates. A recent systematic review of 38 randomised retention trials evaluating six broad types of strategies to increase questionnaire response and retention in randomised trials found that the following strategies may improve questionnaire completion rates: addition of monetary incentives for return of postal questionnaires, recorded delivery of

questionnaires, and a 'package' of postal communication strategies with reminder letters.[37] Given that the trial only involved three sites and 53 participants, caution should be exerted in the use of the study data for estimating rates of recruitment or outcome completion etc. for any future large-scale multi-centre trial. This is supported by the three-fold difference in recruitment between sites 1 and 3 (24 vs. 8 participants). To help address the on-going uncertainty regarding trial feasibility, it is recommended that an internal pilot study be implemented in the first phase of a definitive trial.

There are other difficulties, besides participant recruitment and missing data, which may be faced when setting up and managing a large, multi-centre definitive trial. For example, it may be difficult to recruit a sufficient number of sites that have both an experienced clinician to act as a local Principal Investigator, as well as dedicated exercise facilities with consistent equipment and staffing to ensure treatment fidelity. Regarding the latter, one option may be to pursue delivering the pre-operative exercise programme through existing clinical services, such as cardiac or pulmonary rehabilitation. Other factors that may act as a barrier to the recruitment of sites might include a lack of clinician equipoise and the outcomes of smaller studies inappropriately influencing local commissioning ahead of time (i.e. a definitive study effectively producing redundant outcomes due to already implemented change). In addition, having a large number of trial sites raises logistical issues about maintaining a consistent delivery of the trial protocol and being able to appropriately manage the study data. It may therefore be sensible to enrol a clinical trials unit to manage a future trial, because these units typically have greater capacity, experience and expertise than individual investigators or research teams to manage large-scale trials.

Other factors, besides feasibility and acceptability, need to be considered when deciding whether or not to pursue a full-scale trial. A key factor is whether the evidence base has developed in such a way that an 'evidence gap' no longer exists. The recent study of Barakat et al.[19] warrants discussion in this regard. This study shares many similar features to the present study in that it was a UK-based randomised controlled trial of pre-operative exercise training for patients awaiting elective AAA

repair (endovascular or open). However, notable differences include the greater sample size (124 vs. 53), recruitment from a single site, the lower rate of endovascular procedures (37% vs. 58%), and the use of a circuit-style, moderate-intensity aerobic and resistance training programme delivered thrice weekly for 6 weeks. The authors reported significant improvements in anaerobic threshold and peak oxygen uptake in exercise versus control in a subset of 48 participants who completed repeat CPET assessments, and a significant reduction in the primary outcome of a composite of post-operative cardiac, pulmonary, and renal complications: 22.6% (n=14 complications) in exercise versus 41.9% (n=26) in control. No adverse events were recorded, and it was concluded that "An exercise programme should be considered in all patients before AAA repair". Although the present study was underpowered to support or refute this recommendation, the outcome data do raise some important questions about the appropriateness of the exercise programme. For example, as there were no substantial group-level effects on cardiorespiratory fitness or post-operative clinical outcomes, one may suggest that a 6-week programme of mixed aerobic/resistance training (e.g., Barakat protocol) is superior to a 4-week programme of HIT. Recent studies have shown that short-term pre-operative interval training programmes can improve cardiorespiratory fitness in lung cancer[38] and rectal cancer[39] patients. The current analysis also indicated that about half of the participants were possibly-to-very likely positive responders to this type of training, at least in terms of change in anaerobic threshold. Accordingly, it appears premature to completely rule out HIT as a prehabilitation strategy in the AAA population. A problem that should not be ignored, however, is that many participants may be limited in their ability to perform high-intensity exercise, typically because of safety criteria limiting exercise progression. Therefore, it might be that longer-duration moderate-intensity training is preferential for such patients, at least for ensuring that the exercise 'dose' is delivered as planned. Alternatively, a mixture of interval- and continuous-type exercise may also be worth considering. Indeed, a recent crossover study showed that the incidence of non-response to exercise training may be reduced by changing from interval- to continuous-type training, or vice versa.[41] In terms of extending the duration of the exercise programme, the national 8-week

referral-to-treatment rule obviously imposes restrictions. However, there should be scope to intervene earlier in the surveillance population; for example, starting prehabilitation when AAA diameter exceeds 4.5 cm rather than waiting until aneurysm repair is indicated (i.e., AAA >5.5 cm). Regardless of the optimal timing and content of a pre-operative exercise programme for this population, it seems that a large, multi-centre trial that is pragmatic in design and explores both clinical- and cost-effectiveness is needed before recommendations can safely be made about whether or not the healthcare systems should adopt this type of intervention.

In conclusion, the study highlights where threats to internal and external validity may arise in any future studies of similar pre-operative exercise programmes in similar contexts. Overall, the findings support the feasibility and acceptability of both the pre-operative exercise programme and the trial procedures. An appropriately-powered, multi-centre trial is required to establish the clinical and cost-effectiveness of the intervention.

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Conflicts of interest

None.

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FIGURE LEGENDS

Figure 1. Study assessment schedule (Re-published with permission from Tew et al.[22])

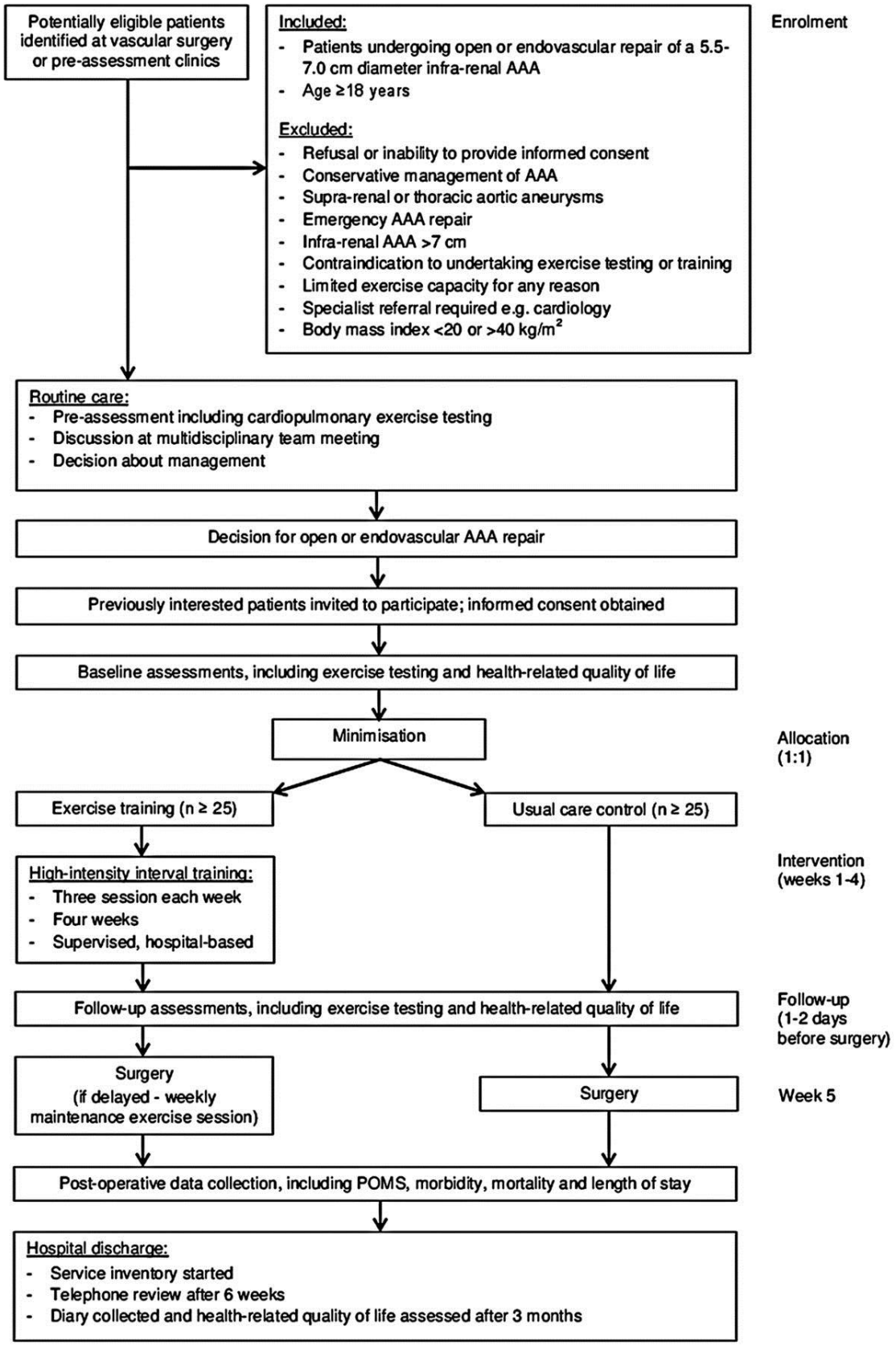

Figure 2. The flow of participants through the trial.

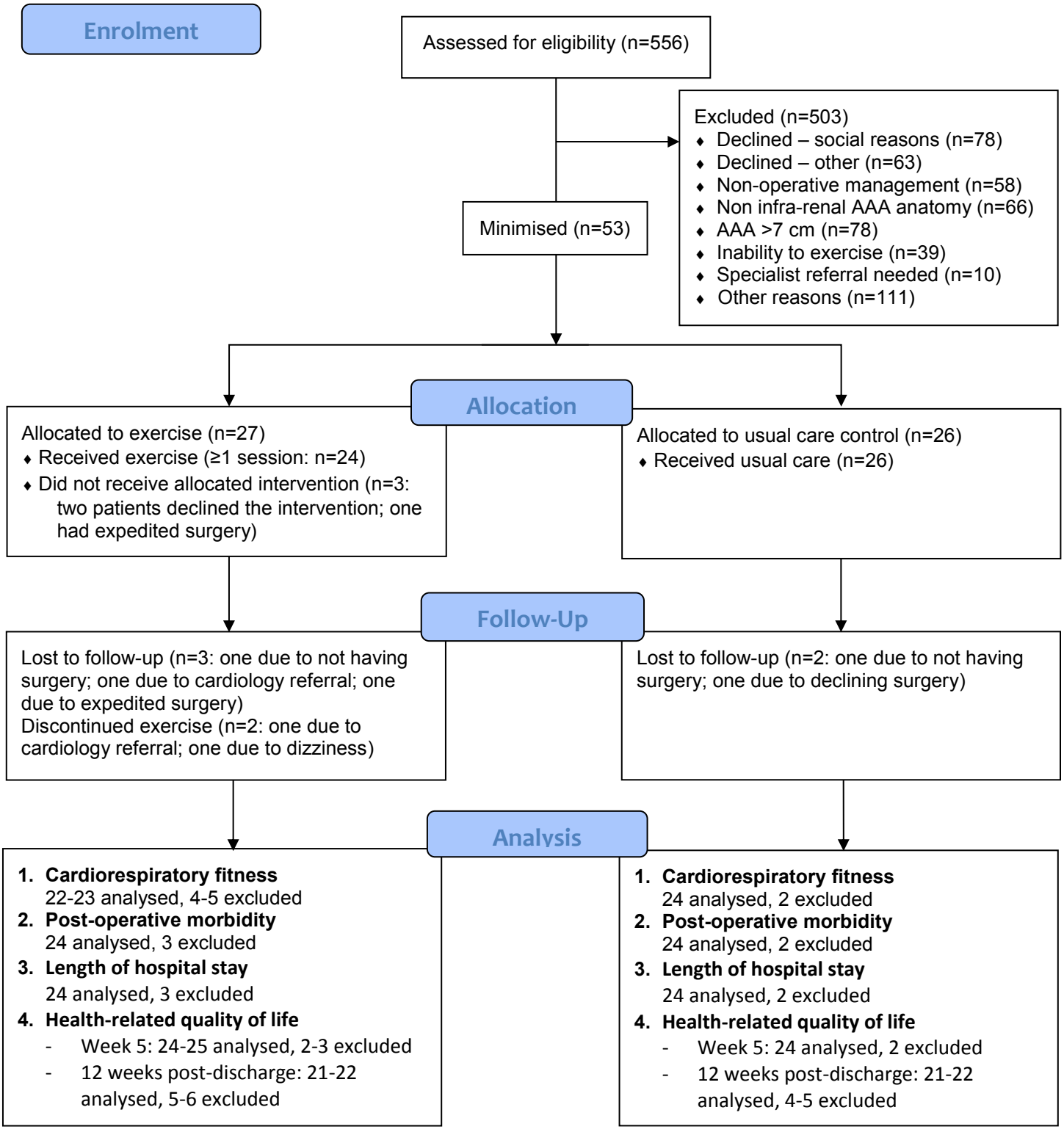

Table 1. Baseline characteristics of participants.

Characteristic	**Exercise (n=27)**	**Control (n=26)**
Age, years	74.6 ± 5.5	74.9 ± 6.4
Sex, number male/female	25/2	25/1
Body mass index, kg/m^2	26.5 ± 4.1	26.8 ± 3.4
AAA diameter, cm	6.0 ± 0.4	5.8 ± 0.4
Repair procedure, number Open/EVAR	11/16	11/15
Current or recent (<6 months) smoker, %	30	8
Comorbidities		
Coronary artery disease, %	41	54
Cerebrovascular disease, %	26	27
Peripheral arterial disease, %	0	8
Diabetes mellitus, %	15	8
Chronic obstructive pulmonary disease, %	22	27
Medications		
Anti-platelet, %	44	42
Statin, %	74	88
ACE-inhibitor, %	54	33
Beta-blocker, %	33	35
Calcium channel blocker, %	26	38
Diuretic, %	4	19
Anaerobic threshold, mL/kg/min	11.0 ± 2.1*	10.9 ± 2.7†
Peak oxygen uptake, mL/kg/min	16.5 ± 3.7*	15.7 ± 3.1
SF-36 Physical Component Summary	50 ± 7*	48 ± 8†

SF-36 Mental Component Summary	57 ± 6	53 ± 10
EQ-5D utility index	0.812 ± 0.155	0.822 ± 0.157
EQ Visual Analogue Scale	73 ± 17	73 ± 16†

Data are mean ± SD unless otherwise stated.

*Based on N=26.

Table 2. Summary of trial feasibility and acceptability data

Methodological issues	Findings	Evidence
1. What factors influenced eligibility and what proportion of those screened were eligible?	Ineligibility for minimisation was mainly due to patient refusal and non-suitable AAA characteristics	240 out of 556 screened were eligible The most common reasons for non-consent were social reasons (e.g., work commitments or difficulty travelling; n=78), AAA diameter >7 cm (n=78), and non infra-renal AAA anatomy (n=66)
2. Was recruitment successful?	Recruitment was to time and target	53 participants were recruited within the 21-month recruitment period
3. Were eligible patients recruited?	Low conversion to recruitment	53 (22%) minimised out of 240 eligible patients
4. Were participants successfully minimised and did minimisation yield equality in groups?	Minimisation process worked well	Similar sized groups, well-balanced on minimisation and other variables
5. Were blinding procedures adequate?	Where used, blinding worked well	Self-reported evidence from research nurses and investigators suggests blinding of POMS assessment and CPET reading was successful
6. Did participants adhere to the intervention?	Good attendance rate, however, the intensity of exercise was generally lower than intended	Overall attendance rate = 76% 17 (63%) out of 27 participants achieved the pre-specified adherence criterion Based on RPE-L, only 30% of work intervals were in the “hard” to “very hard” range
7. Was the intervention acceptable to the participants?	Data from exercise participants suggests the intervention was acceptable, however, the low recruitment rate suggests some problems	30 (64%) out of 47 participants expressed a preference to exercise before minimisation Mean PACES score for exercise participants was 98 out of 119 (SD 19), equating to 'enjoyable'
8. Was the intervention safe?	Our preliminary safety data appears favourable	One non-serious adverse event: short-lived angina Maximal AAA diameter measurements at baseline and week 5 were 6.0 (SD 0.4) cm and 5.9 (SD 0.4) cm, respectively (n=22)
9. Were outcome assessments completed?	Outcome completion rates were generally good, however, missing data for post-discharge questionnaires approached 20%	See results text and Figure 2
10. Was it possible to calculate intervention and healthcare utilisation costs?	Yes	Cost of exercise programme: £1,176 per participant Total costs per participant were £12,519 (SD 3,107) and £12,010 (SD 3,107) for exercise and control, respectively
11. Was retention to the study good?	Retention was good	Retention rate = 91%
12. Were the logistics of running a multi-centre trial assessed?	Some sites recruited better than others. The lead site – where the Chief Investigator and Trial Manager were based – recruited the most participants.	Site 1: 24 participants recruited Site 2: 21 participants recruited Site 3: 8 participants recruited
13. Did all components of the protocol work together?	Components had strong synergy	There were no major difficulties identified in the various processes and the researchers’ ability to implement them. For example, if participants were recruited, they were easily

	minimised and their care moved forwards to the appropriate trial arm.

Methodological issues based on Shanyinde et al.[40]
AAA, abdominal aortic aneurysm; CPET, cardiopulmonary exercise testing; POMS, Post-Operative Morbidity Survey; RPE-L, rating of perceived exertion for legs; SD, standard deviation

Table 3. Summary of cost data in both groups from an NHS and personal social services perspective

	Exercise	**Control**	**Bootstrapped mean difference (95% CI)**
Cost of exercise programme	£1,176 ± 0	£0	£1,176 (N/A)
Costs of AAA repair	£10,481 ± 2,247	£10,880 ± 2,209	-£399 (-1,719 to 1,000)
Post-discharge costs	£862 ± 2,653	£1,129 ± 2,290	-£267 (-1,622 to 1,312)
Total costs	£12,519 ± 3,107	£12,010 ± 3,107	£510 (-1,393 to 2,498)

Data are bootstrapped mean ± SD unless otherwise stated.

SUPPLEMENTARY MATERIAL

METHODS

Sample size

The sample size for a feasibility study should be adequate to estimate critical parameters with sufficient precision. Herein, the critical outcome was adherence to the exercise intervention. A patient was deemed compliant if they completed ≥75% of the scheduled sessions, that is, 9/12 sessions for a 4-week intervention, plus all once-weekly maintenance sessions if surgery was delayed. Success with respect to adherence was defined as a lower limit of 0.67 (c. 2/3 of the population) for the 90% CI for the proportion of the exercise group complying with the intervention. It was estimated that ≥85% of the exercise group would be 'compliers' based on pilot studies in patients with small AAA.[1,2] A 90% CI for a single proportion around a value of 0.85 is 0.68–0.95, with n=25 patients. Using a 1:1 allocation ratio, 25 patients was required for each trial arm; 50 in total.

Methods for quantifying inter-individual differences in the fitness response to the exercise programme

Inter-individual differences in the fitness response to the exercise programme (treatment heterogeneity) were quantified using previously described methods.[3] Briefly, we used linear mixed modelling to derive the standard deviation for individual responses from the difference in response variance (post-pre intervention) between arms. A substantially larger response variance in the intervention group versus control indicates individual differences in response to the intervention. For each patient in the intervention group, we then derived the probability that the individual was a positive responder, trivial responder, or negative responder, where a positive response was defined as a true change > the minimum clinically important difference (MCID). Herein, we assume an MCID of 1.5 mL/kg/min for the anaerobic threshold and 2 mL/kg/min for peak oxygen uptake. The probabilities were calculated using a custom spreadsheet,[4] inputting the individual's observed change in outcome, the typical variability in the outcome in the control group, the number of

patients in the control group, and the MCID. Qualitative descriptors were assigned to the probabilities according to the following scale: <0.005, most unlikely, almost certainly not; 0.005-0.05, very unlikely; 0.05-0.25 unlikely, probably not; 0.25-0.75, possibly; 0.75-0.95, likely, probably; 0.95-0.995, very likely; >0.995, most likely, almost certainly.[5]

Methods for the Economic Evaluation

Identification and measurement of resource use

Resource use was captured for three elements. Firstly, the resources utilised in delivering the exercise programme were micro-costed and estimated on a per-patient basis for those in the exercise group. The exercise programme costs included the capital costs of the exercise and monitoring equipment, the staff time associated with delivering the exercise sessions, and the travel costs associated with getting participants to and from the exercise sessions. Secondly, resource use for the AAA repair procedures and peri-operative care was documented in study case report forms. Thirdly, post-discharge resource use for all treatment/care related to AAA repair was collected retrospectively for 12 weeks by piloting the use of a self-report Service Receipt Inventory (patient diary) completed by participants at 3, 6, 9 and 12 weeks after discharge. Participants were asked to record the frequency of use of primary care, community-based health and social care services, secondary care and costs borne by themselves and carers as a result of their AAA repair. Primary and community care resources included general practice (GP) and home visits, practice nurse visits at the surgery and district nurse visits in the home. Secondary care resources included in-patient stays, accident and emergency visits, outpatient visits and diagnostic tests. Informal care giving time comprised average time per week spent by family and/or friends helping participants with activities that they would have usually been able to undertake if they had not undergone AAA repair.

Valuation of NHS and informal care-giving resource use

For each trial participant, all components of treatment costs stratified by category of resource use were computed by multiplying units of resource use by their unit costs. These were then summed over all resource use categories to obtain a total cost for each participant both from an NHS and personal social services perspective. This was then used to generate the mean and standard deviation costs per participant in each trial arm, as well as bootstrapped mean differences between trial arms and 95% CI. The unit costs for resources used for the costs of the exercise programme were mainly obtained from the study records. Unit costs for open and endovascular AAA repair procedures were based on NHS National Tariff Schedules: £8,285.56 and £12,675.50, respectively.[6] Unit costs for the health and personal social services used by participants in the 12-week period after hospital discharge were obtained from a range of sources including the Personal Social Services Research Unit's Unit Costs of Health and Social Care 2015 cost compendium[7] and NHS Reference costs for 2015.[6] Capital costs was annuitised over the useful lifespan of the equipment (assumed to be 3 years for the watches and heart rate belts and 8 years for the cycle ergometers) using a discount rate of 3.5%. All unit costs were expressed in GBP (£) and valued at 2015-16 prices.

Calculation of health utilities

In line with NICE recommendations,[8] outcomes in the economic analysis were assessed using a multi-attribute utility measure – the EQ-5D-5L[9] – which was recorded at baseline, week 5, and 12 weeks post-discharge. The responses to the EQ-5D-5L were transformed using a standard algorithm to produce a health state utility score.[10]

RESULTS

Supplementary Table 1. Costs of the exercise programme

Resource use	**Quantity**	**Cost**
Capital costs		
Polar heart rate watches and chest straps	6	£382
Cycle ergometers	6	£1,368
*Nurse staff costs**		
Nurse time	12 hours per patient for 27 patients	£9,856
Nurse time maintenance sessions	36 sessions	£1,095
*Physiotherapist staff costs**		
Physiotherapist time	12 hours per patient for 27 patients	£9,856
Physiotherapist time maintenance sessions	36 sessions	£1,095
Travel costs		
Travel costs (£25 per patient - estimate based on average travel time)	12 return journeys per patient for 27 patients	£8,100

*£30.42 per hour based on Band 7 nurse[11]

Supplementary Table 2. Costs per resource use category after hospital discharge using all available data

Cost Item	Exercise (n=21)	Control (n=22)
GP contact at practice	£32 ± 46	£30 ± 37
GP home visit	£7 ± 16	£18 ± 29
GP telephone call	£13 ± 26	£10 ± 26
Practice Nurse contact	£24 ± 58	£11 ± 17
District/Community nurse	£479 ± 1,809	£44 ± 83
Physiotherapy contact	£6 ± 24	£17 ± 68
Occupational therapy contact	£0	£20 ± 64
Dietician contact	£0	£4 ± 18
Hospital out-patient attendance	£417 ± 1,005	£269 ± 200
Accident and emergency attendance	£0	£12 ± 38
Hospital in-patient admission	£0	£693 ± 2,280
Social worker contact	£4 ± 18	£4 ± 17

Data are mean ± SD

GP, general practice

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